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Genomic testing for the causes of stillbirth should be considered for routine use

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Miscarriage and stillbirth are devastating events, and today, around 25 percent of these perinatal deaths are unexplained despite autopsy. Discovering the cause of such a loss is of great importance for the bereaved parents, both in providing an explanation and in helping them to understand the likelihood of a recurrence in future pregnancies. Researchers in Australia have used state of the art genetic testing in order to to help provide answers in such cases.

Associate Professor Christopher Barnett, a clinical geneticist and head of the Paediatric and Reproductive Genetics Unit at the Women's and Children's Hospital, North Adelaide, will tell the European Society of Human Genetics conference today (Monday) how he and colleagues are using whole exome sequencing (WES) and whole genome sequencing (WGS) to detect causes of neonatal death in cases in which it previously remained unidentified. Using data from 43 families referred to the genetics unit, where samples were available from both parents and the fetus (the prospective cohort), and 60 from stored autopsy samples from the fetus or newborn (the retrospective cohort), the researchers were able to uncover an underlying genetic cause in 23 percent of the prospective cohort, and have found a single promising candidate in a further 26 percent.

Solved cases included new disease gene discoveries, new syndrome identification and novel severe fetal presentations of existing rare paediatric disease. In the retrospective cohort, strong candidates for the cause of death were found in 18 percent of cases.

"This study has contributed directly to the birth of healthy babies," Prof Barnett will tell the conference. "We have had numerous couples who, with successful preimplantation genetic diagnosis via in vitro fertilisation in subsequent pregnancies, or through prenatal testing during pregnancy, have been able to avoid the genetic condition experienced in a prior pregnancy. Of course, this can only be offered to couples if a definitive genetic diagnosis is made in the earlier affected pregnancy, and this is the primary aim of our study. These conditions are often extremely rare and, indeed, in some cases they are totally new. "

According to the World Health Organisation, in 2009 there were 2.6 millions stillbirths (the death of the fetus at or after 22 weeks of pregnancy) across the world, with more than 8200 deaths per day. Among the 133 million babies born alive each year, 2.8 million die in the first week of life.

In Australia, a standard perinatal autopsy is done in about 60 percent of cases of unexplained fetal or neonatal death and termination of pregnancy for congenital abnormalities. Some genetic testing is done, but it is limited, usually to chromosomal analysis. As in most other countries, specific genetic sequencing is not a standard part of the autopsy process and when it does occur it is generally limited to a particular condition or a relatively short list of genes. " We are offering the testing of all human genes so that we can increase the rate of diagnosis as much as possible," says Prof Barnett.

One of the main ethical features of the study is that it involves testing the parents as well as the fetus/newborn. This means that the consent procedure needs to be rigorous, and occur in a face to face setting with the clinical geneticist at the time of the counselling that is provided for follow-up of the first autopsy. The genetic diagnoses of the parents may have the potential to affect their health later in life, and the consent process allows them to opt out from knowing these results if they so

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"Our results provide new insights into the molecular mechanisms of early development. We are not surprised that a significant proportion of 'unexplained' fetal and newborn deaths and congenital abnormalities have an underlying genetic cause, and we believe that genomic autopsy should be used routinely in the investigation of pregnancy loss and perinatal death, " Prof Barnett will conclude.

Chair of the ESHG conference, Professor Joris Veltman, Director of the Institute of Genetic Medicine at Newcastle University in Newcastle, United Kingdom, said: "It is often unclear what the cause is of pregnancy loss or the death of a newborn baby. This work shows how state-of-the-art genomic testing can be used as part of the routine autopsy procedure to reveal a genetic cause in up to a quarter of all neonatal cases. A genetic diagnosis can be used to prevent complications in future pregnancies and provide much needed answers to the families involved."

More information: Abstract no: C15.5. The Genomic Autopsy Study: using genomics as an adjunct to standard autopsy to unlock the cause of complex fetal and neonatal presentations

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